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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/802,249

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Ralf Mauritz

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EXAMINER

LIU, SUE XU

ART UNIT

PAPER NUMBER

1639

MAIL DATE

DELIVERY MODE

05/15/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/802,249	Applicant(s) MAURITZ ET AL.	
	Examiner SUE LIU	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 February 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 12, 13 and 15-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 12, 13 and 15-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/12/08 has been entered.

Claim Status

2. Claims 4-11, 14 and 23-26 have been cancelled as filed on 2/12/08.
- Claims 1-3, 12, 13, and 15-22 are currently pending.
- Claims 1-3, 12, 13 and 15-22 are being examined in this application.

Election/Restrictions

3. Applicant's election without traverse of Group I (Claims 1-22) in the reply filed on 10/18/06 is as previously acknowledged.
4. Applicant's election without traverse of the following species:
- A.) nucleic acids for the biopolymers;
 - B.) fluorescent groups, specifically, stilbene, as the detectable protecting groups;
 - C.) Compound (f) in Figure 5 as the core structure;
- in the reply filed on 10/18/06 and 3/6/07 is as previously acknowledged.

Priority

5. This application claims foreign priority to EPO 03006098.2 (3/19/03).
6. Receipt is as previously acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections Withdrawn

7. Upon further consideration and in light of applicants' amendments to the claims, the following claim rejections as set forth in the previous office action are withdrawn:

A.) Claims 1-3, 12, 13 and 15-22 are rejected under **35 U.S.C. 102(b)** as being anticipated by Wagner et al (Helvetic Chimica Acta. Vol. 80: 200-212. 1997; cited in IDS filed on 9/22/04).

B.) Claims 1-3, 12, 13 and 15-22 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Wagner et al (Helvetic Chimica Acta. Vol. 80: 200-212. 1997; cited in IDS filed on 9/22/04), in view of Hobbs et al (5,151,507; 9/29/1992) and if necessary, Chen et al (Journal of Organic Chemistry. Vol. 66: 1725-1732; 2001).

C.) Claims 1-3, 12, 13 and 15-22 are rejected under **35 U.S.C. 103(a)** as being unpatentable over McGall et al (US 6,238,862; 05/29/2001), Wagner et al (Helvetic Chimica Acta. Vol. 80: 200-212. 1997; cited in IDS filed on 9/22/04), in view of Hobbs et al (5,151,507; 9/29/1992) and if necessary, Chen et al (Journal of Organic Chemistry. Vol. 66: 1725-1732; 2001).

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter Rejection

9. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The previous rejection is maintained for the reasons of record as set forth in the Office action as well as the reasons below.

Claim 22 has been amended to recite “wherein B is selected from the group consisting of adenine (A), guanine (G), cytosine (C), aza analogs, deaza analogs of A, G., and C, combination aza an deaza analogs of A, G, and C and analogs thereof containing additional amino groups” (emphasis added) as filed on 2/18/08. The instant claim 22 as amended can be broadly and reasonably interpreted to mean analogs of “aza analogs”, analogs of “deaza analogs”, etc., which “analog”s of “analog”s do not appear to have support in the instant specification. In addition, the recitation of “combination aza and deaza analogs of A, G, and C” also does not have support in the instant specification.

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If Applicant believes this rejection is in error, applicant must disclose where in the specification support for the entire scope of the amendment(s) and/or new claims can be found. As a result, Claim 22 represents new matter.

Discussion and Answer to Argument

10. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants assert support for the instant claim 22 as amended has support at paragraph [0030] of the instant specification. (Reply, pp.5-6).

However, paragraph [0030] of the instant specification only recites “nucleobase analogs”, “aza analogs”, “deaza analogs”, or “nucleobase analogs” having additional amino groups, which recitation does not provide support for the claimed “analogs thereof containing additional amino groups”. That is the cited paragraph [0030] does not appear to have support for the claimed “analogs” of “aza analogs”, analogs of deaza analogs, etc.

New Claim Rejections

Claim Rejections - 35 USC § 112

Second paragraph of 35 U.S.C. 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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12. Claims 1-3, 12, 13 and 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by applicant's amendments to the claims.

Claim 1 has been amended to recite "carrying out a determination of a degree of deprotection by detecting detectable protecting groups remaining on the array after cleavage," which is unclear. The said recitation is in conflict with step (b) of the instant claim 1, which step recites "cleaving off the detectable protecting groups". It is not clear how all the cleaved off "detectable protecting groups" are still "remaining" on the array after cleavage and can be "detected" after the cleavage. Thus, one of ordinary skill in the art would not be able to apprise the metes and bounds of the instant invention.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

McGall and Others

15. Claims 1-3, 12, 13 and 15-22 are rejected under **35 U.S.C. 103(a)** as being unpatentable over McGall et al (US 6,238,862; 05/29/2001), Wagner et al (Helvetic Chimica Acta. Vol. 80: 200-212. 1997; cited in IDS filed on 9/22/04), in view of Hobbs et al (5,151,507; 9/29/1992; cited previously) and if necessary, Chen et al (Journal of Organic Chemistry. Vol. 66: 1725-1732; 2001; cited previously) and Agris (PGPUB 20020045167; 4/18/2002).

The instant claims recite a “quality control method for manufacturing a biopolymer array, the method comprising (a) synthesizing a plurality of different biopolymer species on an array from monomeric or oligomeric building blocks comprising detectable protecting groups, (b) cleaving off the detectable protecting groups, and (c) carrying out a determination of a degree of deprotection by detecting detectable protecting groups remaining on the array after cleavage, wherein steps (a), (b), and (c) are performed on the array and wherein at least some of the detectable protecting groups directly couple to and protect nucleobase amino groups.”

McGall et al, throughout the patent, teach methods of quality control for manufacturing nucleic acid probe arrays (e.g. Abstract and Claim 1 of the reference), which reads on the quality control method of **clm 1**.

The reference teaches synthesizing nucleic acids using protected monomers (e.g. Claims 5, 12 and 23; col. 2, lines 40+; Figure 9), which reads on step (a) of **clm 1** and nucleic acids of **clm 12**.

The reference teaches “deprotecting” (or removal) of the protecting group (e.g. Claim 23; col. 2, lines 40+; Figure 9), which reads on step (b) of **clm 1**.

The reference teaches “determining the amount of unprotected active sites” (col. 2, lines 49+) by detecting the amount “detectable labels” on the array (col. 2, lines 40+; cols. 8-9; Figure 7; especially, col.9, lines 9+), which reads on step (c) of **clm 1**.

The reference teaches the detectable label (or protecting label) is a fluorescent label such as a rhodamine (e.g. Claims 26 and 27 of the reference), which reads on the “fluorescent groups” of **clm 2** and rhodamine of **clm 3**.

The reference teaches the fluorescent label is linked (or coupled) to the nucleotide (e.g. Figure 6), which reads on the “coupled to nucleobases” of **clm 13**. The instant specification and/or claims do not specifically define the phrase “coupled to nucleobase”. The phrase can be broadly interpreted to mean coupling the “protection group” (e.g. fluorescent label) and the “nucleobase” through any type of linkage (including both direct and indirect linkage). The reference teaches linking the fluorescent label through the phosphate group in the sugar group of the nucleotide (e.g. Figure 6), and thus the label is “coupled” to the nucleobase of the nucleotide.

McGall et al do not explicitly teach the protection groups are directly coupled to and protect the nucleobase amino groups as recited in the amended **clm 1**. The reference also does not teach using “stilbene” (the elected species) as the “fluorescent group”, as recited in **clm 3**. The reference also does not explicitly teach the various chemistries recited in **clms 15-22**.

However, **Wagner et al**, throughout the publication, teach methods of nucleic acid synthesis using protected nucleotides. (see Abstract). The reference teaches synthesis of various oligonucleotides using protected nucleotides (pp. 204-206; especially Table 1 and p. 204, last para). The reference teaches the fluorescent label is linked directly to the

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nucleobase (e.g. p. 202, Schemes 1-2), which reads on the “coupled to nucleobases” of **clm 13**, and coupling through the amino groups of **clm 1**. The reference also teaches detecting the protecting groups attached to the synthesized oligonucleotides (e.g. pp.206-207).

The reference teaches the detectable label (or protecting label) is a fluorescent label such as a “dnseoc” (or a “dansyl”) (e.g. p. 201, para 3 and Figures), which reads on the “fluorescent groups” of **clm 2** and “dansyl” of **clm 3**. The “dnseoc” ((dansylethoxy)carbonyl) group also reads on the “L” group when n=1 (as recited in **clm 21**), because the carbonyl group reads on the formula “C(O)” and the dansyl group reads on formula “R”.

The reference also teaches the structure of nucleotides comprising a base (protected by dnseoc), a sugar, a protected hydroxyl group, and a protected phosphate group (e.g. Scheme 2, Scheme 5). The (MeO)₂TrO (or Dimethoxytrityl) group in Scheme 5 of the reference (see p. 201, para 4 and p. 204) reads on the hydroxyl protection group, DMTrO (the elected species of ; see Reply, filed 3/6/07, p. 2) or the “triphenylmethyl” group of **clms 15, 16, and 17**.

The reference also teaches phosphate protection group such as the “(2-cyanoethoxy)bis(diisopropylamino)phosphine” at the 3’ sugar position (p. 204, para 1 and Scheme 5), which is the same phosphoramidite (phosphate amide) (i.e. the R3, R4, R5 and R6 groups of compound (f) in Figure 5 (the instant elected species; Reply, filed 3/6/07)), as recited in **clms 18, 19, and 20**.

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The reference also teaches various nucleobases such as C, A, and G (e.g. p. 204, Scheme 5), which read on the nucleotide bases recited in **clm 22** and the elected species of adenine.

Agris, teach methods of monitoring the degree of deprotection “after” synthesis of oligonucleotides on arrays by detecting detectable protecting groups “remaining on the array” (e.g. Abstract; claims 14 and 50; p.9, [0158]+). The reference also teaches the need for such detection so that simple and reliable techniques for determining the purity of the desired oligonucleotides can be carried out (e.g. p.1, [0005]).

Hobbs et al teach using various fluorescent molecules to label (or protect) nucleotides (see Abstract). The reference teaches “stilbene” can be used to attach to the nucleobases (col. 30, lines 20+) through linkers that comprise “carbonyl” group (reads on the formula of “COR” of **clm 21**; col. 11, lines 50+). The reference also teaches various fluorescent dye can be used depending on the different applications (cols. 12+).

In addition, **Chen et al**, teaches attaching “stilbene” to nucleosides (see Abstract). The Chen reference also teaches “stilbene” has “bright fluorescence of very high quantum yield” (p. 1725, right col., para 2).

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to attach a fluorescent group such as “stilbene” to a “monomeric building block” (such as a nucleoside) to the amino groups of the nucleobase for various assays such as detecting the attached fluorescent group on an oligonucleotide array.

A person of ordinary skill in the art would have been motivated at the time of the invention to couple the protection group to the amino group of the nucleobase, because

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the nucleobase protection groups offer the advantages of providing more efficient and fast working oligodeoxyribonucleotide synthesis, as taught by Wagner et al (e.g. p.200). A person of ordinary skill in the art would also have been motivated at the time of the invention to directly detect the remaining detectable protecting group on an array to assess the purity of the synthesized oligonucleotides, because Agris teaches the need for such as a simple and reliable technique to control the quality of the synthesized microarray, as discussed supra. In addition, it would have been prima facie obvious for a person of ordinary skill in the art to use fluorescent groups (such as stilbene) as the protecting group and to measure the remaining fluorescent signals after cleavage to assess the degree of protection, to improve the quality control assay for the deprotection step during an array generation (of methods such as McGall et al) for the predictable result of enabling routine oligonucleotide synthesis on an array with various known protection and labeling groups.

A person of ordinary skill in the art would have been motivated at the time of the invention to use “stilbene” as the “detectable protecting group”, because “stilbene” is a known fluorescent label for biomolecules (especially nucleotides), and stilbene is known to exhibit “bright blue fluorescence of very high quantum yield”, as taught by both Hobbs et al and Chen et al.

A person of ordinary skill in the art would have been motivated at the time of the invention to use the specific nucleotide building blocks and their corresponding chemistry to generate the required reagent for the method of detecting deprotection, because the structures for basic nucleotide building blocks are known in the art, and the various protection groups are known and routine in the art as taught by Wagner et al. In

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addition, Wagner et al also teach the advantages of using these nucleotide building blocks and their corresponding protection groups, including providing efficient and fast working oligonucleotide synthesis as well as fast and effective cleavage of the protection group (e.g. pp.200-201).

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since McGall et al, Wagner et al, Hobbs et al and Chen et al have demonstrated successful attachment of various protection groups such as fluorescent groups (especially stilbene) to nucleosides through known reaction mechanisms (such as the formation of -HN-C=O linkage between the nucleobases and the stilbene molecule) as well as using various nucleotide building blocks to build oligonucleotides, as demonstrated by the said references.

Discussion and Answer to Argument

16. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

In general, applicants traversed the above rejection over a combination of references by attacking each reference alone. (Reply, pp.10+).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue the McGall reference does not teach “feedback potential”, “overall fluorescence is measure”, “fluorescence is re-measured”, etc.. (Reply, p.11, para 3).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., “feedback potential”, “overall fluorescence is measure”, “fluorescence is re-measured”, etc.) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants are respectfully directed to the above rejection for detailed discussion of how the combination of cited references renders the instant claimed invention obvious.

Applicants also argue the Wagner reference fails to teach “on-array” or “on-chip” analysis (Reply, p.11, para 4).

However, the McGall reference teaches on-array determination of protection and deprotection as discussed above. The combination of the cited references renders the instant claimed invention obvious.

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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Examiner, Art Unit 1639
5/9/08